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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/559,001	04/21/2000	Joan C. Egric	A-460A	1458

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EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 05/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/559,001	EGRIE ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *49 and 50* is/are allowed.

6)☒ Claim(s) *45-48 and 51-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/4/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Status of Application, Amendments and/or Claims

The amendment filed 05 March 2004 has been entered in full. New claims 61-78 were added. Claims 45-78 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

The information disclosure statement filed 20 January 2004 was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits.

Withdrawn Objections And/Or Rejections

The rejection of claims 45 and 51-60 are under 35 U.S.C. 102(b) as being anticipated by Elliott *et al.,* WO 95/05465 (reference submitted by Applicant, IDS #BC, Paper No. 5), as set forth at pages 5-6 of the previous Office Action (18 July 2003) is *withdrawn* in view of Applicants' amendment (20 January 2004).

The rejection of claims 53, 54 and 56 under 35 U.S.C. 103(a) as being unpatentable over Elliott *et al.*, (WO 95/05465, IDS #BC) in view of Yoshitomi *et al.,* US Patent No. 5,559,093, as set forth at pages 6-8 of the previous Office Action (18 July 2003) is *withdrawn* in view of Applicants' amendment (20 January 2004).

The rejection of claims 55 under 35 U.S.C. 103(a) as being unpatentable over Elliott *et al.*, (WO 95/05465, IDS #BC) in view of in view of Igari *et al,* US Patent No.

5,416,071, as set forth at pages 8-9 of the previous Office Action (18 July 2003) is *withdrawn* in view of Applicants' amendment (20 January 2004).

The rejection of claim 57 is rejected under 35 U.S.C. 103(a) as being unpatentable over Elliott *et al.,* (WO 95/05465) in view of Young *et al.,* US Patent No. 6,548,653 B1 as set forth at page 9 of the previous Office Action (18 July 2003) is *withdrawn* in view of Applicants' amendment (20 January 2004).

The rejection of claims 58-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elliott *et al.*, (WO 95/05465) in view of Kawaguchi *et al.,* US Patent No. 4,806,524, as set forth at page 10 of the previous Office Action (18 July 2003) is *withdrawn* in view of Applicants' amendment (20 January 2004).

The objection of claims 47 and 48 as set forth at page 11 of the previous Office Action (18 July 2003) is *withdrawn* in view of Applicants' convincing arguments (20 January 2004).

Claim Rejections - 35 USC § 112, First Paragraph, Written Description, New Matter

Claims 45, 51-65, 69-78 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The specification as originally filed does not provide support for the invention as now claimed: "at about position 114" (claim 45). Applicant's amendment, filed 26 August 2002, asserts that no new matter has been added, but does not provide sufficient direction for the written description for the above-mentioned "limitations". The specification as filed does not provide a written description or set forth the metes and bounds of this "limitations". The instant claims now recite limitations which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as-filed.

Applicant is required to cancel the new matter in the response to this Office action. Alternatively, Applicant is invited to provide *specific* written support for the "limitations" indicated above or rely upon the limitations set forth in the specification as filed.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

Claims 45-48 and 51-78 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The basis for this rejection is set forth at pages 3-5 of the previous Office Action (15 June 2001, Paper No. 13).

Applicants state that the Examiner has not established a prima facie case of non-enablement and that the Examiner appears to suggest that the rejected claims are

directed to amino acid changes at any position in human erythropoietin provided such changes provide an N-linked glycosylation site. Applicants argue that claim 45, as amended, is directed to a new N-linked glycosylation site at about position 114, rather than at any position. Applicants contend that claim 45 would not require one to generate an infinite number of derivatives as is alleged by the Examiner and that the scope of the claim (and the scope of enablement which is required) is different from that alleged by the Examiner. Applicants state that the scope of Claim 45 is enabled, as the specification contemplates and teaches the introduction of new N-linked glycosylation sites in human erythropoietin at about position 114. In view of these extensive teachings, the working examples in the present application and the state of the prior art relating to introduction of new glycosylation sites in human erythropoietin, undue experimentation would not be required.

Applicants state that the Examiner's arguments relating to alleged lower *in vitro* activity of certain hyperglycosylated EPO analogs disclosed in the application do not support the case for nonenablement. Applicants state that the data represented in Table 2 (page 36) indicate that none of the amino acid changes that were made to create new N-linked glycosylation sites abolished *in vitro* activity and only two of 13 analogs showed any reduction in *in vitro* activity. Applicants argue that the specification clearly sets forth guidance for making a number of new N-linked glycosylation analogs that retain some or all of the *in vitro* activity of rHuEPO. Applicants note that one analog (N53) which was observed to have somewhat reduced *in vitro* activity actually had significantly greater *in vivo* activity than rHuEPO (Figure 3 and Example 3). Applicants

state that this suggests that even though *in vitro* activity of a glycosylation analog may be reduced, *in vivo* activity in the same analog can be enhanced.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons.

Claims 45, 46 (and dependent claims) are not enabled because the claims encompass the introduction of N-linked glycosylation sites not taught by the specification. The claims read on human erythropoietin analogs having **one or more (one, two, three or four or more) additional glycosylation sites** as compared to human erythropoietin **provided that one of the sites is introduced at any of the specified positions (52, 53, 55, 86 and/or 114).** Contrary to Applicants' assertion, claim 45, as amended, is directed to an N-linked glycosylation site at about position 114, **and any other position.**

In addition, the instant claims recite "at about position 114" which also encompass the introduction of N-linked glycosylation sites not taught by the specification. "At about position 114" reads on new N-linked glycosylation sites being made at positions 100, 102, 104, 113, etc., because these positions are "at about position 114". The specification is not enabling for this limitation.

The decrease in *in vitro* activity of certain hyperglycosylated EPO analogs, as taught in the specification, supports the case for lack of enablement because it demonstrates that changes made in certain residues of erythropoietin can affect the biological activity (such as N59). It also demonstrates the unpredictability of making residue changes and the need to screen the analogs for *in vitro* and *in vivo* activity. As

Applicants have pointed out, N53 was observed to have reduced *in vitro* activity, but greater *in vivo* activity when compared to rHuEPO.

Lastly, new claims 61-64 (depend from claim 45) and new claims 65-68 (depend from claim 46) recite 2 to 4 (or more) additional glycosylation sites. These claims encompass the introduction of glycosylation sites at any position because the claims fail to recite *where* the glycosylation sites are being introduced. The claims encompass the introduction of any number of glycosylation sites. The claims also fail to recite whether N-linked or O-linked carbohydrates are attached to said glycosylation sites. The working examples in the instant specification teach how to make and use *specific* hyperglycosylated EPO analogs. The specification lacks guidance and working examples regarding how to introduce a glycosylation site at any position in EPO. Furthermore, scientific literature relating to the introduction of new glycosylation sites in human EPO would not be obvious, because one skilled in the art would recognize the unpredictability of the effects of mutations on protein function and structure. There is a large quantity of experimentation necessary to generate the number of derivatives recited in the claims because the specification fails to teach *where* additional glycosylation sites are being introduced and *the number* of additional glycosylation sites being introduced. Based on these reasons, the claims remain non-enabled. The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Claim Rejections - 35 USC § 112, First Paragraph, Written Description

Claims 45-48 and 51-78 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification provides insufficient written description to support the genus encompassed by the claims. The instant claims are directed to encompass analogs of human erythropoietin (SEQ ID NO:1) not supported by the specification (one or more amino acid changes which provide for additional glycosylation site(s), glycosylation sites introduced at about position 114, etc). None of these sequences meet the written description provision of 35 USC 112, first paragraph.

The specification does not place any limit on the number of amino acid changes that may be made to human erythropoietin (SEQ ID NO:1), fails to specifically teach amino acid residue positions, and whether the amino acid changes provide for N-linked or O-linked glycosylation. The specification states that these types of changes are routinely done in the art and provides a table of potential amino acid substitutions, but does not provide any guidance as to what changes should be made and which regions of the instant protein are functionally and structurally critical. There is no description of variants (amino acid changes/substitutions) of SEQ ID NO:1 that exist, while still maintaining function. The disclosure fails to provide a representative number of species to describe the genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

The skilled artisan cannot envision the detailed chemical structure of the encompassed human EPO analogs, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, *only human erythropoietin analogs of SEQ ID NO:1 as specifically taught in the instant specification*, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Allowable Subject Matter

Claims 49 and 50 are allowable.

Conclusion

Claims 45-48, 51-78 are rejected.

Claims 49 and 50 are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RMD
5/3/04

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER